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Trends in serotypes and sequence types among cases of invasive pneumococcal disease in Scotland, 1999–2010

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ABSTRACT

Introduction: The 7-valent pneumococcal conjugate vaccine (Prevenar®, Wyeth; PCV7) was introduced to the UK paediatric immunisation schedule in 2006. This study investigates trends in serotypes and multi locus sequence types (STs) among cases of invasive pneumococcal disease (IPD) in Scotland prior to, and following, the introduction of PCV7.
Methods: Scottish Invasive Pneumococcal Disease Enhanced Surveillance has records of all cases of IPD in Scotland since 1999. Cases diagnosed from blood or cerebrospinal fluid isolates until 2010 were analysed. Logistic and poisson regression modelling was used to assess trends prior to and following the introduction of PCV7.
Results: Prior to PCV7 use, on average 650 cases of IPD were reported each year; 12% occurred in those aged <5 years and 35% affected those aged over 65 years. Serotypes in PCV7 represented 47% of cases (68% in <5 year olds). The serotype and ST distribution was relatively stable with only serotype 1 and associated ST 306 showing an increasing trend. PCV7 introduction was associated with a 69% (95% CI: 50%, 80%) reduction in the incidence of IPD among those aged <5 years, a 57% (95% CI: 47%, 66%) reduction among those aged 5–64 years but no significant change among those aged 65 years and over where increases in non-PCV7 serotypes were observed. Serotypes which became more prevalent post-PCV7 are those which were associated with STs related to the PCV7 serotypes.
Conclusions: Routine serotyping and sequence typing in Scotland allowed the assessment of the relationship between the capsule and the clones in the post vaccination era. Changes in the distribution of serotypes post PCV7 introduction appear to be driven by associations between serotypes and STs prior to PCV7 introduction. This has implications for the possible effects of the introduction of higher valency vaccines and could aid in predicting replacement serotypes in IPD.

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1. Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is responsible for a substantial burden of disease, accountable for approximately 1.6 million deaths annually worldwide [1]. In developed countries, the incidence of invasive pneumococcal disease (IPD) is between 8 and 75 cases per 100,000 individuals [2], with studies showing that most IPD is attributable to only 20–30 of the 94 pneumococcal serotypes [3].

Recent studies of serotypes involved in IPD compare pre- and post-vaccination periods to examine changes in serotype distribution potentially due to the use of the 7-valent pneumococcal conjugate vaccine (PCV7). The USA, and other countries subsequently, showed great reductions in IPD not limited to vaccine targeted groups [4]. However, increases in IPD caused by non-PCV7 serotypes, in particular 19A, following PCV7 use have been documented [4–10].

The pneumococcal capsule is thought to be the main determinant of carriage prevalence and invasiveness and hence the determinant of prevalence amongst disease isolates [11,12]. However, it has been speculated that increases in serotype 19A IPD in particular are perhaps attributable to a capsular switch event after being found associated with a sequence type (ST), ST695, previously only linked with vaccine serotype 4 [13,14]. Other studies have documented increases due to the expansion of multi-drug resistant STs such as ST276 and ST320 [15,16]. Thus, it is increasingly important to examine both STs and serotypes involved in IPD to determine the potential effectiveness of serotype-specific pneumococcal vaccinations.

In September 2006, PCV7 was introduced to the National Health Service childhood immunisation schedule in the UK in a three dose programme at age 2, 4, and 13 months, with a catch-up for those aged up to 2 years. In 2010, 94% of the targeted group had received three doses of PCV7 [17].

This study examines trends in serotype and ST distributions prior to PCV7 use in Scotland, adding to existing reports on the pre-vaccine period in Scotland [18,19]; the effect of PCV7 on IPD incidence; trends in serotype and ST distribution post-vaccination; and the association between serotype and ST pre- and post-vaccination.

2. Methods

2.1. Data

The Scottish Invasive Pneumococcal Disease Enhanced Surveillance (SPIDER) database contains all cases of IPD, identified by blood or cerebrospinal fluid, in Scotland from 1999–2010. The serogroup responsible for each case of disease was available for all years; serotype and ST information was available from 2002.

Clinical isolates (from blood or cerebrospinal fluid) of *S. pneumoniae* were sent to the Scottish Haemophilus, Legionella, Meningococcus and Pneumococcus Reference Laboratory (SHLMPRL) after identification at diagnostic microbiology laboratories. These were grown on Columbia blood agar (Oxoid, UK) at 37 °C under anaerobic conditions using an anaerobic pack (Oxoid, UK) and after a single subculture were stored at −80 °C on Protect beads (M-Tech Diagnostics, UK). Isolates were serotyped by a coagglutination method [20]. Multi-locus sequence typing was performed as described previously [21–23].

Epidemiological years from winter of one year to the end of autumn of the next were used ensuring winter seasons were grouped together since IPD predominantly occurs in winter.

Serotypes and STs were classified according to their joint occurrence prior to PCV7 use (1999–2005) and emergence post-PCV7 (2006–2010). STs were classified as associated with PCV7 serotypes if they occurred at least once in conjunction with a PCV7 serotype (labelled PCV7-ST); otherwise they were classified as not associated (NonPCV7-ST). STs which only occurred following PCV7 use were classified as PostPCV7-ST. The PCV7-ST group was subdivided into two groups: one with12 STs (9, 36, 113, 124, 138, 156, 162, 176, 205, 206, 246, 311) with a high frequency of co-occurrence with the PCV7 serotypes (labelled HF PCV7-ST), and a larger group with low frequency co-occurrence (LF PCV7-ST). Serotypes were categorised in four groups: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F); serotypes not in PCV7 but associated with STs linked through co-occurrence to PCV7 serotypes (PCV7-ST serotypes); serotypes not in PCV7 and not associated with STs linked to PCV7 serotypes (NonPCV7-ST serotypes); serotypes which only occurred post-PCV7 vaccination (PostPCV7 serotypes).

2.2. Statistical analysis

Logistic regression models were used to test whether or not there was evidence of a linear trend in the pre-PCV7 (1999/00–2005/06) serogroup, serotype and ST distributions. Serogroups, serotypes and STs responsible for ≥1% of IPD were considered. Analyses were conducted for the serogroups for age groups 0–4, 5–64, and ≥65 years separately. Bonferroni adjusted confidence intervals were calculated and the Benjamini and Hochberg adjustment for multiple testing used in determining the significance of the trend [24]. The Benjamini and Hochberg adjustment was used since no particular hypothesis about which serotypes or STs would have a trend was specified. As >20 serotypes and STs were examined, the standard 5% level would be more likely to report significant trends for one serotype or ST even if no trend was present.

Poisson regression models were used to assess changes in IPD incidence. The percentage change in the incidence of PCV7 serotypes and NonPCV7 serotypes from the pre-vaccine to the post-vaccine period was assessed by predicting post-vaccination incidence, allowing for a trend in the pre-vaccination years, and comparing the observed cases with the predicted as suggested elsewhere [25,26]; 95% confidence intervals were used. Cases with missing age (27, 0.4%) were omitted. For 637 cases (10.1%), no information on the serogroup was available. The number of vaccine type (VT) or non-vaccine type (NVT) serotypes was imputed, separately by year and age group, using observed proportions of VT serotypes. Imputation of serotype, from serogroup, was carried out when serotype information was not available based on observed proportions of serotypes within serogroups from 2002–2006, separately by age group. All analysis was conducted using R versions 2.8–2.12 [27].

3. Results

3.1. Trends in serotype and ST distributions prior to PCV7

From 1999/00–2005/06, on average 650 IPD cases per year were reported in Scotland, rising from 538 in 1999/00 to 743 in 2002/03. A subsequent drop occurred, primarily amongst those aged ≥65 years, following the introduction of the 23-valent pneumococcal polysaccharide vaccine (PPV23) for this age group in 2003, with a coverage of ∼74%. The number increased to 739 in 2005/06. IPD was most common amongst the elderly (44% of all cases). 12% of cases affected those aged <5 years.

3.2. Serogroup analysis

Thirty-six different serogroups were identified in IPD from 1999/00–2005/06. Serogroup 14 was most common, accounting

Table 1
Results from A) the logistic regression models of serogroups and STs responsible for at least 1% of IPD between 1999/00 and 2005/06 and between 2003/04 and 2005/06, respectively; B) the logistic regression models of serotypes and STs responsible for at least 1% of IPD between 2006/2007 and 2009/2010, examining evidence of significant trends in the proportion of IPD attributable to each serogroup, serotype and ST.

Part A: Serogroup	Count	OR	95% CI	*p*-value	ST	Count	OR	95% CI	*p*-value
14	673	0.94	(0.883, 0.997)	0.003	9	213	1.06	(0.804, 1.402)	0.539
9	364	0.97	(0.892, 1.047)	0.230	306	174	1.40	(1.042, 1.869)	0.001
1	331	1.36	(1.238, 1.493)	<0.001	162	145	1.03	(0.741, 1.432)	0.797
6	301	0.97	(0.891, 1.057)	0.328	53	126	1.01	(0.700, 1.464)	0.924
19	290	0.98	(0.900, 1.074)	0.595	180	96	1.01	(0.678, 1.508)	0.939
4	273	1.04	(0.946, 1.134)	0.284	191	95	1.24	(0.823, 1.875)	0.134
8	247	0.95	(0.865, 1.044)	0.135	124	85	1.00	(0.658, 1.515)	0.987
23	242	0.94	(0.858, 1.035)	0.084	218	74	1.24	(0.784, 1.956)	0.183
3	220	1.00	(0.902, 1.100)	0.917	199	68	0.72	(0.444, 1.151)	0.045
7	162	1.04	(0.926, 1.167)	0.357	227	63	1.22	(0.750, 1.990)	0.244
18	158	0.98	(0.876, 1.104)	0.685	311	63	0.92	(0.561, 1.498)	0.615
12	131	1.04	(0.914, 1.183)	0.400	246	58	0.97	(0.593, 1.601)	0.883
22	107	0.98	(0.849, 1.125)	0.648	433	48	0.60	(0.314, 1.132)	0.022
20	83	0.95	(0.808, 1.113)	0.360	205	41	1.21	(0.654, 2.228)	0.386
33	71	0.94	(0.789, 1.110)	0.285	176	41	1.18	(0.620, 2.237)	0.468
11	65	0.97	(0.811, 1.160)	0.638	206	40	1.22	(0.652, 2.271)	0.372
15	51	1.01	(0.829, 1.239)	0.864	113	38	1.02	(0.530, 1.965)	0.930
					235	35	0.77	(0.390, 1.531)	0.284
					36	32	1.19	(0.572, 2.475)	0.499
					138	30	1.16	(0.581, 2.295)	0.552
					62	30	1.14	(0.531, 2.429)	0.636
					65	25	1.63	(0.691, 3.838)	0.106

Part B: Serotype	Count	OR	95% CI	*p*-value	ST	Count	OR	95% CI	*p*-value
1	210	0.71	(0.58, 0.86)	<0.001	306	139	0.73	(0.58, 0.92)	<0.001
8	162	0.85	(0.68, 1.05)	0.026	191	217	1.16	(0.96, 1.39)	0.026
7F	240	1.11	(0.93, 1.34)	0.091	53	123	0.90	(0.71, 1.14)	0.195
3	173	1.00	(0.81, 1.23)	0.997	180	135	1.08	(0.86, 1.35)	0.343
19A	165	1.40	(1.11, 1.75)	<0.001	199	128	1.25	(0.98, 1.58)	0.008
22F	130	1.34	(1.04, 1.72)	<0.001	433	88	1.51	(1.12, 2.04)	<0.001
12F	79	1.10	(0.81, 1.49)	0.372	218	59	1.00	(0.72, 1.40)	0.995
6A	74	0.86	(0.63, 1.17)	0.161	227	46	0.85	(0.58, 1.25)	0.238
9 N	48	0.90	(0.62, 1.32)	0.434	62	45	1.15	(0.78, 1.69)	0.306
11A	54	1.08	(0.75, 1.56)	0.514	235	23	0.80	(0.47, 1.36)	0.232
20	35	0.64	(0.40, 1.02)	0.005	65	23	0.74	(0.43, 1.28)	0.119
33F	43	1.13	(0.75, 1.70)	0.397					
15B	31	1.16	(0.72, 1.89)	0.362					
23A	28	0.96	(0.58, 1.57)	0.800					

Note: Count is the number of serogroups and STs among IPD cases in the pre-PCV7 period in Part A and serotypes and STs among IPD cases in the post-PCV7 period in Part B; OR–Odds Ratio associated with a one year change; CI-95% Bonferroni adjusted confidence interval; *p*-value is the unadjusted *p*-value. The entries in bold typeface are those with *p*-values below the Benjamini and Hochberg adjusted *p*-value.

for 17% of IPD cases, followed by serogroups 9 (9%) and 1 (8%). Serogroup 1 replaced 14 as the most common in 2005/06. The proportion of serogroup 1 IPD increased steadily over the pre-PCV7 study period, with evidence of an increasing trend ($p < 0.001$) (Table 1, Part A). Serogroup 14 was borderline significant after adjustment for multiple testing, with a decreasing trend from 1999/00–2005/06.

3.3. Serotype analysis

From 2003/04–2005/06, 42 serotypes were identified in IPD. PCV7 serotypes accounted for 47% of cases in this period; 68% of cases in those <5 years, 40% and 48% in those 5–64 years and ≥65 years, respectively. The most common serotypes, 14 (15%), 1 (13%), 4 (7%), 9V (7%), 8 (6%), 3 (6%), 23F (5%), 6B (4%), 7F (4%) and 19F (4%), were responsible for 71% of IPD.

Evidence of an increasing trend in serotype 1 IPD was found ($p = 0.029$). No other serotypes were found to have significant trends.

3.4. ST analysis

The most common STs in IPD from 2003/04–2005/06 were 9 (9%), 306 (9%), 162 (6%), 53 (5%), 180 (4%), 191 (4%), 124 (4%), 218 (3%), 199 (3%) and 227 (3%). ST9 was commonly associated with serotype 14; ~60% of serotype 14 IPD during this period was ST9. ST306 was commonly associated with serotype 1. There were 158 STs in IPD in 2003/04, 140 in 2004/05 and 115 in 2005/06, showing a reduction in diversity over time.

There was evidence of an increasing trend in ST306 IPD from 2003/04–2005/06, compared to the 0.05 significance level (Table 1, Part A). No other STs showed strong evidence of a trend.

3.5. The effect of PCV7 on IPD incidence

From 2006–2010, 2380 cases of IPD were reported. 140 cases occurred in those aged <5 years, 1239 in those 5–64 years, 1001 in those ≥65 years. Following PCV7 use, PCV7 serotype IPD incidence declined by 97.4% in children under 5 (Table 2). Among those aged 5–64 years and ≥65 years, a significant reduction of VT IPD of 86.3% and 80.4%, respectively, was observed. For those <5 years and 5–64 years, there was no significant increase in NVT notifications in 2008/09 compared to the predicted incidence (Fig. 1). Among those aged ≥65 years, a significant increase in NVT disease of 46.5% was observed. The reduction in VT incidence and increase in NVT incidence resulted in no change in all-type incidence in this group.

Almost all NVT serotypes exhibited an increase in disease incidence from the last two pre-vaccination years to 2008/09 (7F: 153.6%, 3: 26.2%, 8: 42.5%, 19A: 78.7%, 22F: 151.6%, 6A: 31.8%, 12F: 2.3%, 11A: 73.9%, 9N: 33.3%). The exception is serotype 1 which

Table 2
Incidence rates of the most common non-vaccine type (NVT) IPD serotypes and vaccine type (VT) serotypes in Scotland from 2004/05 to 2009/10.

	Incidence 2004/05 (*n*)	Incidence 2005/06 (*n*)	Incidence 2009/10 (*n*)	Change 2009/10 predicted compared to observed	Change 2009/10 predicted compared to observed (serotype 1 excluded)
0–4 yrs.					
All	38.23 (101)	27.35 (73)	14.18 (41)	−68.5% (−80.4, −50.0)	−69.8% (−81.7, −50.8)
NVT	12.87 (34)	7.12 (19)	13.49 (39)	−39.6% (−71.4, 28.6)	−13.4% (−62.4, 102.7)
VT	25.36 (67)	20.24 (54)	0.69 (2)	−97.4% (−99.6, −91.3)	−97.5% (−99.6, −91.4)
5–64 yrs.					
All	8.11 (324)	9.52 (381)	6.59 (266)	−57.2% (−65.5, −46.9)	−42.1% (−54.1, −26.9)
NVT	4.73 (189)	6.22 (249)	5.92 (239)	−45.6% (−58.3, −29.1)	3.4% (−23.7, 40.3)
VT	3.38 (135)	3.30 (132)	0.67 (27)	−86.3% (−91.6, −78.4)	−87.0% (−92.0, −79.5)
65+ yrs.					
All	31.09 (258)	32.08 (268)	26.48 (230)	−4.9% (−24.4, 19.5)	0.0% (−20.7, 26.1)
NVT	15.06 (125)	17.00 (142)	24.12 (210)	+46.5% (9.0, 97.4)	64.7% (21.4, 124.0)
VT	16.03 (133)	15.08 (126)	2.30 (20)	−80.4% (−88.6, −67.9)	−80.5% (−88.6, −68.0)

Notes: The percentage change is a comparison of the predicted incidence in 2009/10 to the observed incidence in 2009/10 adjusting for the temporal trend pre-vaccination (see Methods). 95% confidence intervals for the percentage changes are derived from the Poisson regression model. When serotype 1 is excluded, the percentage changes for VT differ slightly because inflation in this case is assumed to distribute over all types.

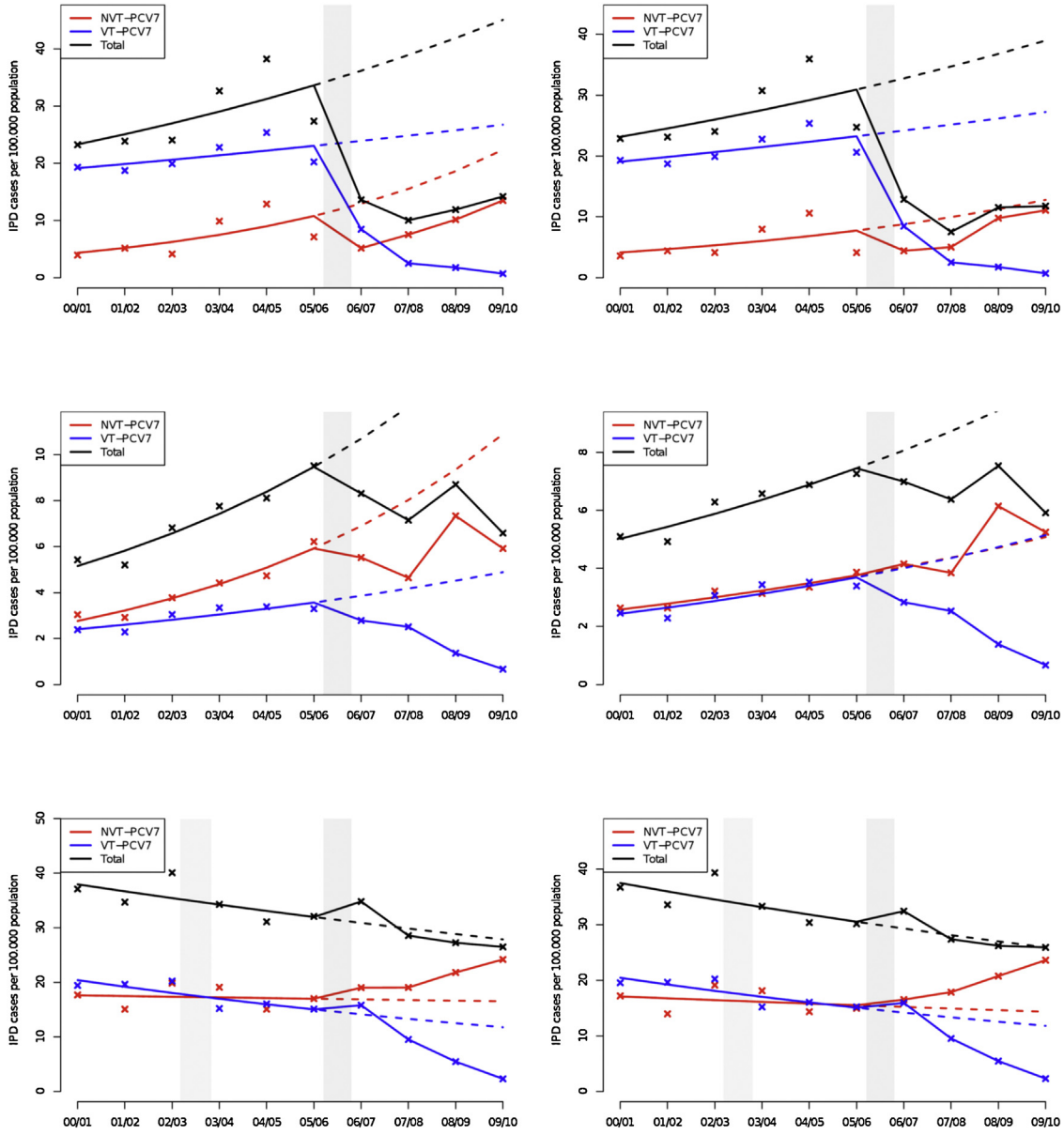

Fig. 1. Incidence rates of vaccine type (VT) and non-vaccine type (NVT) IPD in Scotland, by age group.
Note: All serotypes are included in the left hand column of graphs while serotype 1 is excluded from the right hand column of graphs. The top row are for those aged 0–4 years, the middle row for those aged 5–64 years and the bottom row for those aged 65+ years. The grey vertical bar denotes the introduction of PCV7. For those aged 65+ years, the first grey vertical bar denotes the introduction of PPV23. The data are plotted as crosses, the dashed lines show the predicted post vaccination incidence based on pre vaccination trends and the predicted values from the poisson regression model are the points joined by the lines.

Table 3
The association between ST and serotype among IPD cases in Scotland in the period prior to the introduction of PCV7 in September 2006.

		STs associated with PCV7 serotypes													STs not associated with PCV7 serotypes
		HF PCV7-ST [12 STs]												LF PCV7-ST [154STs]	Non PCV7-[151 STs]
PCV7/Serotypes		9	36	113	124	138	156	162	176	205	206	246	311	269 entries	0
	PNE004	0	0	0	0	0	0	0	0	40	37	56	0		
	PNE06B	0	0	0	0	25	1	0	37	0	0	0	0		
	PNE09V	0	0	0	1	0	13	102	0	0	1	0	0		
	PNE014	208	0	0	84	0	4	1	0	0	0	0	1		
	PNE18C	0	0	36	0	0	0	0	1	0	0	0	0		
	PNE19F	1	0	0	0	0	0	35	0	0	0	0	0		
	PNE23F	0	32	0	0	0	0	0	l	0	0	0	62		
PCV7-ST serotypes	25 Serotypes not in PCV7 but associated with the STs linked to PCV7	25 entries over all 25 serotypes and all 12 sequence types												683 entries	353 entries
NonPCV7- ST serotypes	22 differentSerotypes not associated with any ST linked to PCV7	0												0	145 entries

Serotypes not in PCV7 but associated with the STs linked to PCV7:.
PNE001, PNE003, PNE005, PNE008, PNE020, PNE034, PNE038, PNE06A, PNE07A, PNE07C, PNE07F, PNE09A, PNE09N, PNE11A, PNE15A, PNE15B, PNE15C, PNE16F, PNE17F, PNE18B, PNE18F, PNE19A, PNE22F, PNE33C, PNE33F.
Serotypes not associated with any ST linked to PCV7:.
PNE002, PNE013, PNE021, PNE024, PNE027, PNE029, PNE031, PNE037, PNE041, PNE042, PNE10A, PNE10F, PNE12A, PNE12B, PNE12F, PNE18A, PNE22A, PNE23A, PNE24F, PNE28F, PNE35B, PNE35F.
STs in the HF PCV7-ST group had more than 10 reports of co-occurrence with PCV7 serotypes. There are 779 entries for these 12 STs. In the full matrix there are 1048 reports among 166 STs associated with PCV7.

showed a decrease despite the previously reported increase pre-PCV7. Only increases in 7F (128.5%; 95% CI (30%, 308.8%)) and 22F (126.7%; 95% CI (15%, 356.6%)) were found to be significant when allowing for pre-vaccination trends. The decrease in serotype 1 IPD was mainly driven by those aged <5 years and 5–65 years.

3.6. Trends in serotype and ST distribution post-PCV7

Post-PCV7, serotypes (23B (12 times), 28 (6), 6C (5), 12 (1), 16A (1), 17A (1), and 35C (1); 27 of 2213 isolates typed) and STs (164 STs; 222 of 2203 isolates sequenced) not previously reported in Scotland were noted. 10% of the isolates sequenced were new STs whilst only 1% of the isolates typed gave rise to new serotypes.

Amongst the 14 serotypes each accounting for at least 1% of IPD cases post-PCV7 (Table 1, Part B), there were significant increasing trends in serotype 19A and 22F IPD, at rates of 40% and 34% per year, respectively, and decreasing trends for serotypes 1 and 20, at rates of 29% and 36% per year, respectively.

Eleven STs accounted for more than 1% of all STs reported in IPD post-PCV7. ST306 decreased significantly at a rate of 37% per year, comparable with the decrease in serotype 1. ST199 and ST433 both exhibited significant increases post-PCV7 with 25% and 51% increases per year, respectively. ST199 was principally associated with serotype 19A and, to a lesser extent, 15B whilst ST433 was almost universally associated with serotype 22F. Serotype 20 was principally associated with ST235.

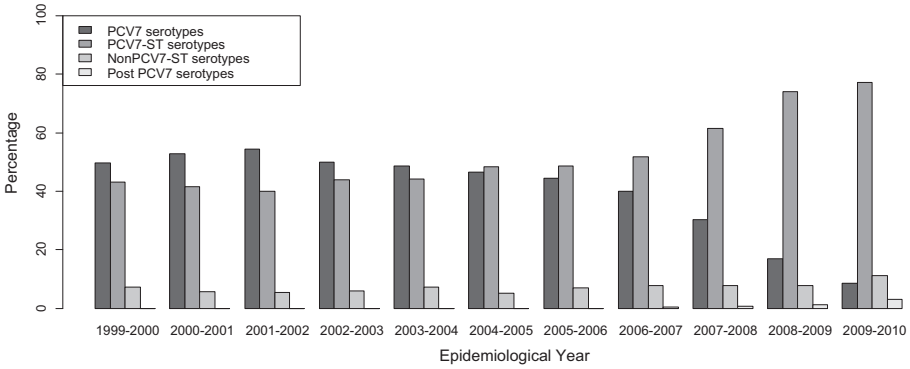

Fig. 2. Trends in the serotype distribution from 1999/2000 to 2009/2010.
Note: In the period 1999–2002 when only serogroup was available, the serotypes of PCV7 serogroups were imputed based upon the distribution of serotypes within serogroups in the period 2003–2006. A sensitivity analysis showed that this had minimal impact on the distributions presented.
PCV7–serotypes in the PCV7 vaccine.
PCV7 serotypes–serotypes in the PCV7 vaccine.
PCV7-ST serotypes–serotypes not in the PCV7 vaccine but which are associated with STs associated with the PCV7 serotypes.
NonPCV7-ST serotypes–the remaining serotypes present among IPD cases prior to the introduction of PCV7. These serotypes are not associated with any ST connected with the 7 PCV7 serotypes.
Post PCV7 serotypes–serotypes which have emerged post PCV7 (post September 2006).

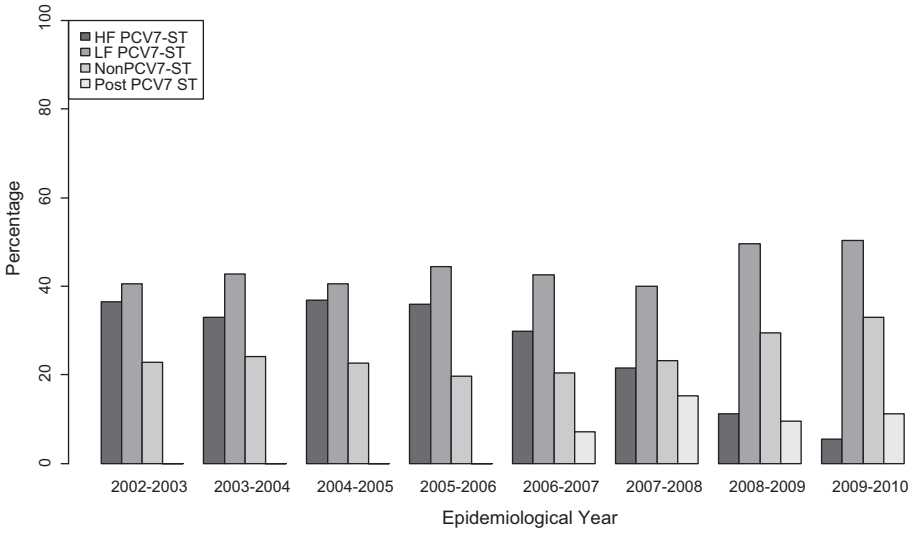

Fig. 3. Trends in the ST distribution from 2002/2003 to 2009/2010.
Note: HF PCV7-ST–The 12 STs with a strong association with the PCV7 serotypes in the PCV7 vaccine. LF PCV7-ST–the remaining STs associated with the PCV7 vaccine serotypes. NonPCV7-ST - STs not associated with any serotype in the PCV7 vaccine.
Post PCV7–STs which have emerged post PCV7 (post September 2006).

3.7. Association between serotypes and STs pre- and post-PCV7

Associations between serotypes and STs in the period prior to PCV7 use are shown in Table 3. PCV7 serotypes were associated with 166 STs, however only 12 STs (9, 36, 113, 124, 138, 156, 162, 176, 205, 206, 246, 311) account for the vast majority (74.3%) of the IPD cases. PCV7 serotypes, associated with these 12 STs (labelled PCV7-HF PCV7-ST), were responsible for 779 IPD cases. Another 269 cases were caused by PCV7 serotypes associated with the remaining 154 STs (labelled PCV7-LF PCV7-ST).

Regarding NVT serotypes associated with the 166 STs linked to PCV7, 25 different serotypes were responsible for 708 IPD cases, of which only 25 were linked with HF PCV7-STs. The other 683 were associated with the remaining 154 low frequency STs (cross-classification of PCV7-ST serotypes and LF PCV7-ST). The 25 PCV7-ST serotypes had associations (353 cases) with 151 STs not directly associated with PCV7 (cross-classification of PCV7 ST serotypes and NonPCV7-ST). Finally these 151 NonPCV7-STs were associated with 22 NonPCV7-ST serotypes (145 cases) with no direct link with any ST linked to PCV7.

Trends in the distribution of groups of serotypes and STs are presented in Fig. 2 and Fig. 3, respectively. Both show a relatively stable distribution in the pre-PCV7 period. The serotype distribution has changed in favour of those serotypes which were associated with STs shown to have had an association with serotypes in PCV7–the PCV7-ST serotypes. Before 2006/07, these serotypes formed ~40% of all serotypes but formed 80% in 2009/10. The NonPCV7-ST serotypes formed 6% of serotypes prior to 2006/07, rising to 8% in 2008/09 and 11% in 2009/10. The ratio of the percentage of NonPCV7-ST serotypes to the percentage of PCV7-ST serotypes has remained relatively constant over the whole period. The ST distribution did not change as dramatically but the 12 HF PCV7-STs decreased while the remaining LF PCV7-STs and STs not associated with PCV7 increased by about 10% each. New post-PCV7 STs accounted for ~10% of STs in 2009/10. There was some evidence of Simpson's Paradox, with the aggregation masking differing trends in the serotype–ST association. Further examination showed that the rise in LF PCV7-STs was associated with PCV7-ST serotypes while the rise in the NonPCV7-STs is more associated with PCV7-ST serotypes than NonPCV7-ST serotypes.

4. Summary

Amongst non-PCV7 serotypes and STs not primarily associated with these serotypes, there was some evidence of a change in the distribution. IPD from NVT serotypes 19A and 22F increased, whilst serotype 20 showed a decrease. Serotypes 19A and 22F were linked to LF PCV7-STs, the group of serotypes which showed an increase. Serotype 20 was not linked to PCV7-STs and, on the whole, this group of serotypes was relatively static compared to PCV7-ST serotypes.

5. Discussion

Prior to routine PCV7 use, the distribution of serotypes and STs in Scottish IPD appeared static, only serotype 1 IPD was found to increase, alongside an increase in ST306 IPD. Routine PCV7 vaccination drastically reduced the burden of VT IPD in Scotland, not only among children targeted for vaccination but also the rest of the population. Little evidence of serotype replacement was found except for the elderly where increases in NVT IPD outbalanced decreases in VT IPD. The major replacement serotypes were 19A and 22F alongside STs 199 and 433. Routine collection of information on both the genetic background and capsular serotype allowed an analysis of relationships in response to vaccine implementation. Interestingly, the proportional increase of serotypes after vaccination was greatly attributable to serotypes which were associated with PCV7 STs. This implies that ST perhaps plays a role in determining the fitness of a pneumococcus and that it may be possible to predict serotypes likely to increase most following the use of increased valency vaccines by examining STs associated with VT serotypes and identifying the NVT serotypes also found to be associated with these STs. It is important to note, however, that STs linked to disease causing serotypes in the developing world may not correspond with those in the developed world (e.g., outbreaks attributable to serotype 1 in sub-Saharan Africa were associated with ST 618 and 217, not 306 and 227 as in the developed world) [28]. Therefore, results presented here may not be applicable worldwide.

Our findings on pre and post-vaccination trends correspond to existing literature. Serotype 1 bacteraemia was found to increase over time in the UK and Ireland [29], as well as serotype 1 IPD

in England and Wales [25]. Furthermore, the increase observed in serotype 19A IPD has been widely observed [13–16,30–32].

Following PCV7 use, VT serotypes were almost eliminated from IPD in those aged <5 years, providing clear evidence of a strong vaccine effect in this group, as has been documented in other countries [33–35]. Furthermore, there appears to be evidence of herd protection in those aged 5–64 years, as well as those aged ≥65 years, corresponding with herd protection observed elsewhere, with sustained benefits of PCV7 use in preventing VT serotypes recently documented [36]. Among those aged ≥65 years, there is evidence of serotype replacement with an increase in NVT incidence, also shown in the USA and elsewhere [37,38]. This serotype replacement may be attributable to PPV23 use; however, the timing of the observed decline does not correspond with this introduction. Among those aged <5 and 5–64 years, serotype replacement is less clear, masked by serotype 1 IPD which was increasing prior to PCV7 use before decreasing. However, adjusting for this, serotype replacement in these groups has been less pronounced in Scotland than reported in England and Wales [25] and elsewhere [39,40]. It is unclear why Scotland is different to England and Wales. One possibility could be replacement in the nasopharynx of Scottish residents by opportunistic NVTs which predominantly cause IPD in those ≥65 years. Studying changes in nasopharyngeal carriage before and after PCV7 use, as done elsewhere [41,42], could shed more light on this. These studies found no reduction in overall carriage due to increased NVT carriage following PCV7 introduction. Huang et al. identified evidence of increased carriage of NVT serotype 29 and an increase in serotype 15; Flasche et al. report increases in carriage of several NVT serotypes (33F, 7F, 10A, 34, 15B, 31, 21, 3, 19A, 15C, and 23A) following PCV7 use. In the UK, serotypes 3 and 19A were the most prevalent IPD causing serotypes in those aged >65 years from 2008–2010 [43], potentially due to increased carriage of these serotypes post-PCV7 introduction. Therefore, it would be of interest to examine changes in serotype carriage post-PCV7 in Scotland.

A strength of this study is that Scottish IPD data can be considered as a complete national data set as >90% of pneumococci isolated from IPD patients in Scotland are sent to the SHLMPRL [44]. Although there has not been an investigation of changes in sensitivity of IPD reporting due to PCV7 use in Scotland, no changes were anticipated as the surveillance system has not altered. By using logistic and poisson regression to model linear trends, evidence of changes in the serotype and ST epidemiology can be identified.

The 13-valent PCV (PCV13) contains the PCV7 serotypes, as well as 1, 3, 5, 6A, 7F and 19A. PCV13 was introduced in the UK in 2010 and should aid in the prevention of further IPD, however as there will be serotypes linked to those in PCV13 through STs associated with PCV13 serotypes, a change in serotype distribution can perhaps be anticipated due to increases in those linked serotypes. Therefore, it is important to continue to monitor STs, as well as serotypes, associated with cases of IPD to aid in determining the long-term effectiveness of serotype-specific vaccine interventions and to guide development of future vaccines.

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